Use of local anesthetics for dental treatment during pregnancy; safety for parturient

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Pregnancy induces significant anatomical and physiological changes in the mother. Many pregnant women need dental treatment due to poor oral hygiene related to pregnancy. However, most dentists are reluctant to provide, and most pregnant women are reluctant to receive, dental treatment during pregnancy. Theoretically, maternally administered drugs are transferred to the fetus. Depending on the types of drugs and the stage of pregnancy, the effects of drugs on the mother, as well as the fetus, may vary. Local anesthetics are the most widely used in dental treatment. It is, therefore, important to understand the potential effects of local anesthetics during pregnancy. In this review, we will focus on the maternal and fetal effects of local anesthetics widely used in dental treatment with consideration of the use of local anesthetics during pregnancy.

Keywords: Anesthetics, Local; Dental Care; Fetus; Pregnancy

INTRODUCTION

Pregnancy is a special experience in the lifetime of a woman. The mother's health is directly connected to that of the fetus, and therefore, it is important for pregnant women to maintain good health. Oral health care is especially important for pregnant women who are soon to be mothers both for their own health and for their fetuses. However, many dentists and pregnant women tend to overlook the importance of oral health care [1]. Many dentists feel reluctant to perform dental treatment on a pregnant woman due to uncertainty about the effects of the treatment on the mother and her fetus. Furthermore, many pregnant women overlook the importance of visiting dentists to receive proper oral health care during the prenatal period [2,3]. Changes in the oral environment and in food consumption during pregnancy can increase the incidence of dental caries [4], while hormone changes increase the incidence of periodontal diseases [5,6]. Poor management of oral heath increases the incidence rates of preeclampsia, preterm birth, and low birthweight [7]. Therefore, it is necessary that oral health be properly managed during pregnancy and treatment be undertaken if necessary.

Local anesthesia is administered in most dental treatments, and theoretically, maternally administered drugs can be transferred to the fetus through the placenta and affect the fetus. Therefore, when performing a dental procedure on a pregnant woman, the effects of any drug administered to the pregnant women must be considered for both the mother and the fetus. In this review, we

discuss a number of considerations that must be made when trying to provide the mother with safe and effective dental treatment using local anesthesia.

PREGNANCY-RELATED PHYSIOLOGICAL CHANGES

Pregnancy begins when a fertilized egg implants onto the uterine wall. As gestational development proceeds, the mother undergoes many changes in physical function. These include various physiological alterations that are necessary for fetal growth and development. The rate and the extent of these changes vary with gestational age. Understanding the normal physiological changes during pregnancy is important when differentiating between pregnant women with pregnancy-related complications and healthy pregnant women.

CHANGES IN CARDIAC FUNCTIONS

Cardiovascular changes are known to begin early in pregnancy. The largest cardiovascular change associated with pregnancy is the dilation of peripheral blood vessels, which reduces systemic vascular resistance [8]. The production and secretion of various factors that induce vascular dilation is known to increase during pregnancy. Cardiac output also increases as a result of increased stroke output rather than increased heart rate.

As the uterus size increases, the inferior vena cava may be compressed by the uterus when the mother is in the supine position; this reduces venous return and, subsequently, cardiac output. Such a phenomenon is called supine hypotensive syndrome. Therefore, it is advised for pregnant women to lie on their side to prevent this compression. Symptoms of cardiovascular diseases are likely to worsen during pregnancy. For women with preeclampsia or eclampsia, their symptoms may drastically worsen due to changes in cardiac function during pregnancy.

CHANGES IN ENDOCRINE FUNCTION AND METABOLISM

Pregnancy can induce diabetes [9]. When glucose production increases in the diabetic mother, an increased amount of glucose gets transferred to the fetus. Glucose promotes the fetal growth, and maintains balance in the mother's nutritional status [10]. Gestational diabetes commonly develops as a result of insufficient production of insulin, which disrupts the balance in the antagonism between insulin and estrogen and progesterone. The risk for gestational diabetes is higher if the mother is obese, or has a family history of type II diabetes.

Levels of triglycerides and low density lipoprotein (LDL) and the production of high density lipoprotein (HDL) increase during pregnancy [9]. LDL plays an important role in the production of steroids in the placenta. Triglycerides can be used as a source of energy by the mother and the fetus when glucose levels are low.

A sufficient protein intake is necessary during pregnancy for healthy fetal development. Amino acids are easily transferred to the fetus through the placenta, and are used in fetal growth and development. Energy is largely obtained from fat rather than from protein catabolism. Thus, protein catabolism decreases during pregnancy.

CHANGES IN RENAL SYSTEM

Due to a decrease in vascular resistance in the blood vessels leading to the kidney during pregnancy, renal blood flow increases, and subsequently, the glomerular filtration rate (GFR) increases. Moreover, there are changes in the rates of resorption and secretion of water and metabolites in the renal tubules [11]. Upon the activation of baroreceptors in response to reduced venous return during pregnancy, the renin-angiotensin-aldosterone system and the sympathetic nervous system become activated [12]. As a result, water and sodium resorption increases, and this induces hypervolemia and hypoosmotic

conditions in the mother [13]. Extracellular fluid volume and plasma volume both increase by over 30% during pregnancy relative to before pregnancy. Blood volume also increases by 45%.

As both the GFR and capillary permeability to albumin increase, protein excretion and excretion of glucose and uric acids also increases. Resorption of these molecules by the renal tubules decreases.

CHANGES IN LIVER FUNCTION DURING PREGNANCY

The secretion of estrogen and progesterone increases during pregnancy, and reaches the maximum rate in the third trimester [14]. These hormones are known to affect liver function [15]. The synthetic ability of the liver can be assessed by measuring albumin levels and prothrombin time (PT). While there is no significant difference in PT during pregnancy, albumin levels decrease. Alpha-1 acid glycoprotein levels also decrease during pregnancy. As a result, unbound forms of administered drugs increase. Such an increase in drug levels leads to increased distribution of drugs within tissues and increased effects of the drugs.

Hepatic blood flow is known to increase 1.5 fold during pregnancy [16]. Such changes in hepatic blood flow can affect the metabolism of drugs that are mostly metabolized in the liver. Theoretically, increased hepatic blood flow during pregnancy can decrease drug bioavailability by increasing drug clearance.

An increase in bile acid levels during pregnancy is known to induce sub-clinical cholestasis. Ultrasound shows an increased fasting gallbladder volume, and an increased residual volume after contraction. However, these symptoms do not occur in most cases, and when they do occur, they disappear after delivery; thus, they do not pose serious clinical problems in most cases.

MATERNAL–FETAL DRUG TRANSFER

The mother and the fetus are connected to one another via the placenta. Nutrients are transferred to the fetus through the placenta, and waste products produced from metabolic processes in the fetus are transferred to the mother for excretion. Drugs administered to the pregnant women may affect the fetus after they are transferred to the fetus through the placenta. Understanding the structure and the function of the placenta is essential for understanding how drugs are transferred from the mother to the fetus.

PLACENTA STRUCTURE AND FUNCTION

The placenta is an important disc-shaped organ that physically connects the mother and the fetus. The most basic structure of the placenta is the chorionic villi. The villi are vascular structures enclosed within the chorion (the outermost fetal membrane). The intervillous space is the space between villi that includes maternal and fetal blood vessels, and has a large cavernous structure. At Week 8 (gestational age), the blood vessels of the mother's uterus reach the intervillous space, which is large enough to contain 400-500 mL of blood. Gases, nutrients, and drugs administered to the mother are transferred to the fetus through the placenta. Essentially, maternally administered drugs can be transferred from the mother to the fetus and affect the fetus.

TRANSFER OF DRUGS THROUGH THE PLACENTA

Although the method of transfer varies, most drugs enter the systemic circulation of the fetus via passive diffusion. Some drugs are transferred to the fetus through various active transporters on the placenta. Drug exchange also occurs via facilitated diffusion, phagocytosis, and pinocytosis [17].

1. Passive diffusion

Passive diffusion is most common type of drug transfer from the mother to the fetus. Drugs are transferred according to a concentration gradient, and no energy is required for the transfer. The amount of drug transferred per unit time is determined by the concentration of the drug in the mother's circulation and the placental properties that affect the drug transfer. Drugs are transferred through the syncytiotrophoblast layer, or via water channels [18].

Passive diffusion is an important mechanism of drug transfer for drugs that have low molecular weights, have high lipophilicity, and are in unionized forms. Structurally, the placenta consists of lipid bilayers and thus lipophilic drugs that are not bound to proteins can freely diffuse across the placenta [19].

Drugs that use passive diffusion are known to follow Fick's law of diffusion. Diffusion rates, which depend on time, are directly proportional to the surface area of the placenta and the concentration gradient, and inversely proportional to the membrane thickness.

2. Facilitated diffusion

Facilitated diffusion requires carrier substances within the placenta. Facilitated diffusion does not require energy, similar to passive transfer. Carrier-mediated transport systems for cephalosporin, cephalexin, and glucocorticoids have been reported [20, 21]. However, drug transfer using facilitated diffusion is rare. Facilitated diffusion is largely used for transfer of endogenous compounds to the fetus to meet its functional metabolic demands [22].

3. Active transport

In active transport, drugs are transferred via protein pumps in the placental membrane. This transfer mechanism requires energy released from adenosine triphosphate (ATP) hydrolysis. Energy generated by an electrochemical gradient resulting from the transmembrane movement of ions may also be used. Carriers are required for drug transfer. Carriers may become saturated, but competitive inhibition by similar compounds does not occur. Active transporters exist in both the mother and the fetus. Drugs are transferred across the syncytiotrophoblast.

THE EFFECTS OF LOCAL ANESTHETICS ON THE FETUS

Drugs administered to the mother are transferred to the fetus through the placenta, although the extent of transfer varies. The effects of transferred drugs on the fetus can vary depending on the drug type and the fetal general conditions. Local anesthetics are the most commonly used types of drugs in dental treatment. Pregnant women are prone to develop dental diseases. Therefore, understanding the effects of local anesthetics on the fetus is crucial for performing safe and effective dental treatments in pregnant women.

Moshira et al. studied toxic effects of the local anesthetics lidocaine and etidocaine, injected into fetal and neonatal lambs. Similar patterns of toxic effects were observed in both groups when the concentration of local analgesic was greater than the toxic concentration [23]. Unlike what had been expected, the toxic effects of the local anesthetics were not more prominently expressed in the neonatal lamb than in the adult sheep. The volume of distribution of drugs is high in fetuses as fetuses have a large distribution of blood vessels, and this may be why fetuses have reduced sensitivity to toxic effects of drugs.

On the other hand, sensitivity to neurologic and cardiovascular toxicity of local anesthetics is increased in fetuses with asphyxia. Binding of local anesthetics to proteins is reduced in a fetus with asphyxia compared to a healthy fetus, and lidocaine becomes trapped as a result of tissue acidosis [24]. Local anesthetics must be used with caution for fetuses at high risk of asphyxia or with poor general conditions since they are likely to experience side effects from local anesthetics.

The severity of the effects of a local anesthetic on a fetus is determined by the amount of local anesthetic delivered across the placenta. The amount of local

anesthetic delivered during local anesthesia is determined not only by the amount of local anesthetic administered, but also the method of administration, whether vasoconstrictors have been used, the metabolic rate and half-life of the local anesthetic in the mother, the extent of fetal and maternal protein binding, and the pKa (acid dissociation constant) of the local anesthetic [25].

Local anesthetics can be classified as two types: ester or amide. Ester-type local anesthetics are hydrolyzed by esterase in the plasma and have a shorter duration of action than the amide-types. Ester-types are rapidly hydrolyzed in the mother's plasma, and thus have few effects on the fetus. Allergic reactions caused by local anesthetics can pose a danger for both the mother and the fetus, and ester-types are more likely to induce these allergic reactions. In comparison, the likelihood of amide-type local anesthetics inducing allergic reactions is very low.

Amide-type local anesthetics, which are widely used clinically, exert different kinds of effects depending on their type. The amount of amide-type anesthetic delivered to a fetus is largely affected by the extent of maternal protein binding. Only free compounds that do not bind proteins are transferred to the fetus through the placenta. Therefore, the fetal-to-maternal ratio of a local anesthetic is determined by the extent of protein binding of the local anesthetic. Among the amide types, bupivacaine is known to have the lowest fetal-to-maternal ratio [26]. Theoretically, bupivacaine should have the smallest effects on the

fetus among all amide types. For this reason, bupivacaine is widely used as a local anesthetic in the field of obstetrics. However, at toxic levels, bupivacaine inhibits cardiac conduction, which leads to cardiac arrest with low chances of survival. For this reason, high-concentration bupivacaine is currently not used to induce local anesthesia in dental treatment.

Lidocaine is the most commonly used local anesthetic in a dental cartridge. The extent of protein binding of lidocaine is smaller than that of bupivacaine. The proportion of free lidocaine is relatively high, so the amount of lidocaine transferred from the mother to the fetus is also relatively high. As a result, lidocaine has a relatively high fetal-to-maternal ratio [26]. Vasoconstrictors are added to lidocaine to reduce the absorption of the local anesthetic, reduce toxicity, and increase the analgesic effects. Epinephrine is commonly added to lidocaine contained in a dental cartridge as a vasoconstrictor. Vasoconstriction induced by epinephrine delays the absorption of local anesthetics by the mother, allowing the absorption of lidocaine to gradually occur in the maternal systemic circulation, while also allowing blood levels of lidocaine to gradually increase. The local anesthetic is transferred to the fetus slowly, and its margin of safety is also increased. Considering how local anesthetics have small direct effects on the fetus even at submaximal doses [27], lidocaine may be considered relatively safe for use in pregnant women. However, epinephrine can reduce blood flow within the uterus to

Table 1. Pregnant risk factor definition [29]

Category	Definition
A	Controlled studies with pregnant women failed to demonstrate a risk to the fetus in the first trimester, with no evidence of risk in later trimesters. The possibility of fetal harm is unlikely.
B	Either animal reproduction studies have not demonstrated a fetal risk and no controlled studies have been conducted in pregnant women, or animal reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies with women in the first trimester and have not found evidence of a risk in later trimesters.
C	Either studies in animals have revealed adverse effects on the fetus (teratogenic, embryocidal, or other effects) and no controlled studies have been conducted in women, or studies in women and animals are not available. Drugs should be given only if the potential benefits justify the potential risk to the fetus.
D	No positive evidence of human fetal risk is found, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
X	Studies in animals or humans have demonstrated fetal abnormalities, or evidence of fetal risk is found based on human experience, or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are, or may become, pregnant.

Table 2. FDA categories and maximal dose of local anesthetics

Drugs	Type	Maximum dosage (with vasoconstrictors) (mg/kg)	Maximum total dosage (with vasoconstrictors) (mg)	FDA category
Lidocaine	Amide	7	500	B
Articaine	Amide	7	−	C
Mepivacaine	Amide	7	550	C
Prilocaine	Amide	6	400	B
Bupivacaine	Amide	−	90	C

an extent that is proportional to its dose and reduce uterine contractile force [28].

The Food and Drug Administration (FDA) has proposed a classification system that classifies drugs according to their risk [29] (Table 1). Drugs under categories A and B are considered to pose no danger to humans. Categories A and B differ by whether the drug has been tested in human subjects or not. Drugs whose teratogenic risk cannot be eliminated are classified under category C. Category D includes drugs with positive evidence of human fetal risk. Drugs in category X are not recommended for use by pregnant women.

The FDA categories and maximal dose of local anesthetics are presented in Table 2 [26,30].

Toxic concentrations of local anesthetics are similar between the fetus and the mother, and the toxicity of drugs is equipotent in the fetus and the mother. When using local anesthetics in pregnant women, the effects of the local anesthetics on the mother and the fetus must be considered, and the drug dose must be determined carefully.

STAGES OF PREGNANCY

The mother and the fetus undergo different changes as pregnancy progresses. Following the implantation of a fertilized egg on the uterine wall, the fetus undergoes various stages of development as gestational age increases. Organs develop in the early pregnancy period, and the formed organs and tissues undergo volumetric growth in the middle and late stages of pregnancy [31]. Therefore, an identical drug may have different effects on the fetus and the mother depending on gestational age.

Understanding the difference in the potential effects of a maternally administered drug according to gestational age will allow local anesthetics to be safely used in dental treatments associated with pregnancy.

FIRST TRIMESTER

Starting from 1 month after fertilization, a closed neural tube, a beating heart, and blood cells form. The embryonic stage is the period until 10 weeks after implantation, and the first trimester is the period until 13 weeks after implantation. During this period, the development of the most important structures is complete, limbs form, and the fetus starts to move. Important structures formed during this period undergo further growth throughout the pregnancy period, and the likelihood of an organ deformity developing after this period is relatively low.

A fetus may develop a birth defect when exposed to chemicals that can induce mutations in the process of cell growth and chromosome proliferation. Organogenesis is actively underway during weeks 4-10 (gestational age), so teratogenic effects may appear upon fetal exposure to drugs during this period. Therefore, postponement of elective dental treatment until the end of the first trimester is generally recommended.

SECOND TRIMESTER

The second trimester is the weeks 14 through 27 in terms of gestational age. The risk of the teratogenic effects of drugs is lower during this period than during

the first trimester. Most dentists tend to be extremely careful about performing dental treatments even during this period [32]. However, elective dental treatment has been reported to be relatively safe during this period. Moreover, as the extent of physiological changes that occur during the second trimester is not too considerable, anesthesia is safer to perform in pregnant women for non-obstetric surgery in the second trimester than in the first or third trimester [33]. However, starting from week 20 (gestational age), the risk of hypotension in the supine position increases because of aortocaval compression. Aortocaval compression also decreases blood flow into the uterus and may negatively affect the fetus. These risks must be considered when performing dental treatments in pregnant women during this pregnancy period.

THIRD TRIMESTER

In the third trimester, aortocaval compression in the supine position is even more likely to occur because of the enlarged uterus. By placing a cushion on one side of the back to support the lateral position, symptoms, including hypotension and light-headedness, that may occur when lying in the supine position can be alleviated. Pregnancy itself can affect neurological function [34]. Furthermore, conduction blockade occurs at a significantly faster rate during pregnancy than when not pregnant [35]. This demonstrates that the effects of local anesthetics may present more prominently as gestational age increases. Use of local anesthetics at low doses may be possible for pregnant women in the third trimester and may reduce the expression of the toxic effects of local anesthetics.

CONSIDERATIONS IN DENTAL TREATMENT DURING PREGNANCY

Research on whether surgical procedures and anesthesia performed on the mother in preparation for non-obstetric treatments induce pregnancy complications and negatively affect the fetus is important for the safety of the fetus and the mother. Poor management of oral health of the mother is reported to increase the incidence of premature birth, geriatric diabetes, and preeclampsia [36-38]; for this reason, proper oral health management during pregnancy is an important issue. The American Congress of Obstetricians and Gynecologists and the American Academy of Pediatrics strongly recommend pregnant women to undergo dental treatment [39]. However, research on whether dental treatment during pregnancy is associated with negative pregnancy outcomes or not is rare. In a study conducted between 1959 and 1965 that involved 60,000 pregnant women, administration of local anesthetics such as benzocaine, procaine, tetracaine, and lidocaine did not increase the incidence of complications in the fetus [27]. In a study on 351 pregnant women who required periodontal and dental treatments, dental treatment was found not to increase the rates of negative fetal and pregnancy outcomes [32]. Hagai et al. recently reported no significant difference in the rate of birth defects of the fetus between pregnant women who were exposed to local anesthetics for dental treatment and those who were not exposed, although 53% of all pregnant women included in this study were exposed to the local anesthetics during the first trimester [40]. These results provide no clear evidence that use of local anesthetics in pregnant women for routine dental treatment increases complication rates for the mother and the fetus. Therefore, dentists who are concerned [3,41,42] and reluctant [2,43] about performing dental treatments in pregnant women should change their perception about dental treatments in pregnant women and believe that women can undergo all necessary dental procedures during pregnancy.

However, special care is needed in many cases. When the dose of a local anesthetic exceeds the maximum permissible dose, toxic reactions may occur. Toxic effects of local anesthetics that are associated with the central nervous system, such as reduced consciousness and seizure, occur first. Seizure during pregnancy is

associated with increased rates of negative pregnancy complications. Following a seizure, catecholamine secretion is increased, and subsequently, blood flow into the placenta is reduced. Systemic seizures can lead to tissue acidosis and hypoxia. Anticonvulsants used to treat seizures can be transferred to the fetus through the placenta and negatively affect the fetus. Therefore, when performing dental treatments in pregnant women, the doses of local anesthetics must be maintained below the maximal permissible dose while negative aspiration is monitored to make sure the local anesthetics are not injected in blood vessels.

Some pregnant women may contract diseases that increase the risk of pregnancy in the second trimester, although most women may not. Diseases that induce hypertension are known to develop in approximately 8% of pregnant women. Major examples of these diseases include preeclampsia and eclampsia. They develop starting at week 20 (gestational age) and are accompanied by hypertension and diabetes. The mother is diagnosed with eclampsia if she experiences a seizure. When the dilation of the blood vessels entering the uterus and, subsequently, placenta perfusion are reduced, complications, including premature birth, may develop. Many pregnant women with hypertensive diseases have poor oral health and require dental treatment during pregnancy [44,45]. However, theoretically, rates of complications associated with the use of local anesthetics are high for these women. Protein binding of local anesthetics is reduced in pregnant women with preeclampsia or eclampsia; therefore, a large amount of local anesthetics can be transferred to the fetus. Moreover, epinephrine included in a dental cartridge can significantly contract the blood vessels inside the uterus and reduce the blood flow to the placenta. Therefore, local anesthetics must be used with caution in pregnant women with geriatric hypertensive diseases.

When local anesthetics are administered to pregnant women with fetal compromise resulting from reduced placenta perfusion, the amounts of local anesthetics not bound to proteins increase, tissue acidosis occurs, and the local anesthetics may get trapped in the fetus, causing complications. Therefore, if the general condition of the fetus is poor because of the mother's pregnancy-related medical conditions, use of local anesthetics at doses that are commonly used may still have negative effects on the fetus. The types and doses of the local anesthetics for dental treatments must be carefully determined for high-risk pregnant women who are likely or are planning to undergo dental treatment during pregnancy.

CONCLUSION

When local anesthetics are administered to pregnant women during dental treatments, both the woman and her fetus become exposed to the local anesthetics. Therefore, the effects of local anesthetics on the mother and the fetus must be considered when planning dental treatments to improve the mother's oral health. Fortunately, lidocaine, which is the most commonly used local anesthetic during dental treatments, is under category B and considered to have almost no negative effect on the mother and the fetus. In addition, the likelihood of the use of local anesthetics in dental treatments for pregnant women negatively affecting the women and their fetuses appears to be low. Therefore, pregnant women are reluctant to undergo and dentists reluctant to perform dental treatments when the oral health of the pregnant women has been compromised by physiological changes related to pregnancy; thus, delaying the needed dental treatment is not advisable. However, as exposure to drugs in the first trimester has a high risk of teratogenic effects, dental treatment is advised only after the second trimester as long as it is a regular and not an emergency treatment. In addition, pregnant women who have contracted medical conditions that can induce serious pregnancy-related complications are also more prone to experience side effects from local anesthetics even at commonly administered doses. Thus, the dose and type of the local anesthetic must be carefully determined for these women.

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